Cytokeratin expression in adrenal phaeochromocytomas and extra-adrenal paragangliomas

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Abstract

**Aim**—To examine whether adrenal phaeochromocytomas and extra-adrenal paragangliomas are immunoreactive for commonly available and routinely used cytokeratin antibodies.

**Methods**—18 extra-adrenal paragangliomas and seven adrenal phaeochromocytomas were stained with CAM 5.2, AE1/3, and 34βE12 following microwave antigen retrieval of formalin fixed tissue.

**Results**—A single case from the cauda equina was positive for both CAM 5.2 and AE1/3. In addition, two other cases—an intravagal and an orbital paraganglioma—also showed strong immunopositivity with CAM 5.2 and AE1/3. All phaeochromocytomas were negative with all epithelial markers.

**Conclusions**—Cauda equina paragangliomas are known to stain with cytokeratins; however, occasional paragangliomas from other sites may also be immunoreactive with cytokeratins. If the results of immunohistochemistry are not interpreted in the clinical and morphological context, the failure to recognise that extra-adrenal paragangliomas may on occasion react with anticytokeratin antibodies may lead to their being confused with metastatic carcinomas.

**Keywords:** paraganglioma; phaeochromocytoma; cytokeratin

The paraganglion system can be divided into (1) the adrenal medulla and (2) the extra-adrenal paraganglion system. The latter can be further subdivided into two components: first, that associated with the orthosympathetic system (occurring in the para-aortic, thoracic, and abdominal regions and functionally related to the adrenal medulla); and second, that related to the parasympathetic system.

Cytokeratin expression has been used to distinguish between paragangliomas, which are negative, and carcinoids and neuroendocrine carcinomas, which are positive. However, paragangliomas of the cauda equina have a distinctive cytokeratin immunophenotype. Paragangliomas from various sites have been examined for a host of neural and neuroendocrine markers, and some of these studies have also looked cytokeratin expression. Thus far, only one study has shown cytokeratin expression in paragangliomas not arising from the cauda equina. The purpose of this paper is to verify those findings, and also to establish if cytokeratin can be identified in phaeochromocytomas of the adrenal gland and in extra-adrenal paragangliomas using commonly available anticytokeratin antibodies.
The adrenal phaeochromocytomas were negative for both CAM 5.2 and AE1/3. Both adrenal and extra-adrenal cases were negative for 34βE12.

The cases that were positive with microwave antigen retrieval were also positive when stained without antigen retrieval, but the degree of staining was less intense.

**Discussion**

Extra-adrenal paragangliomas are unique tumours of the dispersed neuroendocrine system that differ from other tumours of this system in their clinical behaviour. Indeed, the behaviour is site dependent. Extra-adrenal paragangliomas, unlike their adrenal counterparts, rarely result in clinical manifestations related to excess hormone production. Although the majority of paragangliomas are sporadic, they can also be multicentric and familial—that is, they can be part of the multiple endocrine neoplasia syndromes.

Paragangliomas in the head and neck often raise the suspicion of lymphadenopathy from metastatic carcinoma. From a diagnostic point of view this confusion is heightened by cytokeratin expression in occasional paragangliomas. The absence of cytokeratin expression by paragangliomas has been used to separate them from other neuroendocrine tumours. This finding was confirmed and accepted until Johnson and colleagues noted that some head and neck paragangliomas did show cytokeratin immunoreactivity. However, the extent and diagnostic implications of these findings were not developed.

Ultrastructural examination of paragangliomas has not revealed the presence of tonofilaments, although cell adhesion specialisations are seen. These are regarded as modified tight junctions rather than true desmosomes and are the basis for the lack of immunoreactivity with anti-cytokeratin. Paragangliomas of the cauda equina, on the other hand, have been shown to contain cytoplasmic intermediate filaments and thus are immunoreactive for cytokeratins. Cytokeratin immunoreactivity has also been demonstrated in gangliocytic paragangliomas.

Two of 18 paragangliomas not arising from the cauda equina have been found to show intense, diffuse immunoreactivity for both CAM 5.2 and AE1/3. This finding is important from a diagnostic point of view because these lesions may be misinterpreted as carcinomas. However, this can be avoided if paragangliomas are considered in the differential diagnosis and the morphological features are taken into account. Furthermore, one should be aware that very occasional non-cauda-equina paragangliomas express the commonly used antibodies to cytokeratin (CAM 5.2 and AE1/3). Phaeochromocytomas, on the other hand, appear to be negative for both these markers.

The rationale for this immunoreactivity is not readily apparent. This study adds another group of tumours that must be considered when assessing cytokeratin positivity in the diagnostic setting.
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